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EXAMINER	
SINGH, ANOOP KUMAR	

ART UNIT	PAPER NUMBER
1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/637,710	PANDA ET AL.	
	Examiner	Art Unit	
	Anoop Singh	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 May 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-21* is/are pending in the application.

4a) Of the above claim(s) *9-21* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *05/02/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election of invention of group I (claims 1-8) in the reply filed on May 2, 2006 is acknowledged. Because applicant did not specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 9-21 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on May 2, 2006.

Claims 1-8 are under consideration in the instant application.

Claim Objections

Claim 3 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. In the instant case, claims 3 recite the method of claim 1, while claim 1 is directed to a transgenic knockout mouse, which is not a method claim. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-8 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for

(i) a transgenic mouse, wherein said transgenic mouse comprises in its genome a homozygous disruption of the endogenous melanopsin gene such that no functional melanopsin protein is made in cells of the mouse, wherein said mouse exhibits an attenuated circadian rhythm phase shift in response to a monochromatic light pulse during a dark portion of an environmental dark/light cycle, and

(ii) a method for identifying a therapeutic agent for modulating circadian rhythm in a mouse, the method comprising:

-administering an agent to the transgenic mouse comprising comprises in its genome a homozygous disruption of the endogenous melanopsin gene such that no functional melanopsin protein is made in cells of the mouse, wherein said mouse exhibits an attenuated circadian rhythm phase shift in response to a monochromatic light pulse during a dark portion of an environmental dark/light cycle and then

-selecting an agent that modulates the circadian rhythm in said mouse;

does not reasonably provide enablement for any other mouse or any other animal comprising in its genome homozygous or heterozygous deletion of melanospin gene.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

In determining whether Applicant's claims are enabled, it must be found that one of skill in the art at the time of invention by applicant would not have had to perform "undue experimentation" to make and/or use the invention claimed. Such a determination is not a simple factual consideration, but is a conclusion reached by weighing at least eight factors as set forth in In re Wands, 858 F.2d at 737, 8 USPQ 1400, 2d at 1404. Such factors are: (1) The breadth of the claims; (2) The nature of the invention; (3) The state of the art; (4) The level of one of ordinary skill in the art; (5) The level of predictability in the art; (6) The amount of direction and guidance provided by Applicant; (7) The existence of working examples; and (8) The quantity of experimentation needed to make and/or use the invention.

These factors will be analyzed, in turn, to demonstrate that one of ordinary skill in the art would have had to perform "undue experimentation" to make and/or use the invention and therefore, applicant's claims are not enabled.

Furthermore, USPTO does not have laboratory facilities to test if an invention will function as claimed when working example are not disclosed in the specification, therefore enablement issues are raised and discussed based on the state of knowledge pertinent to an art at the time of the invention, therefore, skepticism raised in enablement rejections are those raised in the art by artisan of expertise.

Claims 1-4 are drawn to a transgenic mouse comprising a disruption in an endogenous melanopsin gene, such that no functional melanopsin protein is made in cells of the mouse. Claim 2 limits the transgenic mouse of claim 1 to include homozygous deletion of melanopsin gene. Claim 3 includes attenuated circadian rhythm phenotype in homozygous mouse of claim 1. Claim 4 is directed to a cells isolated from the mouse of claim 1, wherein genome of the cell comprises a disruption in its endogenous melanopsin gene, and wherein the homozygous disruption prevents the expression of a functional melanopsin protein in said cell. Claims 5-8 are directed to a method for identifying a therapeutic agent for modulating circadian rhythm in a mammal by administering an agent to a transgenic knockout animal whose genome comprises a disruption in its endogenous melanopsin gene, wherein the disruption prevents the expression of a functional melanopsin protein in cells of the animal and the animal comprises a homozygous disruption of the melanopsin gene; and selecting an agent that modulates the regulation of circadian rhythm in the animal. Subsequent claims limit the method of claim 5 to include phenotype of the knockout animal showing an attenuated circadian rhythm phase-shift response and selecting step comprising an agent that enhances the animal's circadian rhythm phase-shift response. Claim 8 limits the transgenic animal to include a mouse.

Because these claims encompass an attenuated circadian rhythm phenotype the details of the disclosure provided by the applicant, in view of the prior art, must encompass a wide knowledge so that one of skilled in the art, at the time of invention by applicant, would be able to practice the invention as claimed by the applicant without

undue burden being imposed on such Artisan. This burden has not been met commensurate with full scope of the claims because it would require undue experimentation to establish to produce a transgenic animal compromising a homozygous or heterozygous disruption in endogenous melanopsin gene, wherein the transgenic animal exhibits an attenuated circadian rhythm phenotype as recited in the instant application.

As a first issue, claim 1 embraces a transgenic knockout mouse whose genome comprises a disruption in the mouse's endogenous melanopsin gene, wherein the disruption prevents the expression of a functional melanopsin protein in cells of the mouse. As recited, instant claim reads on a transgenic mouse comprising homozygous as well as heterozygous disruption of melanospin gene. In addition, claims 1-2 and 4 do not recite any specific phenotype associated with the transgenic knockout mouse. The specification teaches melanopsin knockout mice showing no immunostaining for melanopsin in Opn4-/- mice while Opn4+/+ and Opn4+/- mice show anti-melanopsin immunoreactive. It is further noted that Opn4-/- mice show no detectable defect in locomotor activity rhythms when placed in constant darkness (Figure 2 A and B). However, these mice show a significantly attenuated phase delay in comparison to the wild type animals (Figure 3). It is noted that the phase delay was significant at sub saturating irradiance of light, while only a slight attenuation of the phase shift was seen at higher irradiance in the knockout animals (pages 28-30 pf the specification). The art teaches the feasibility of creating a homozygous disruption of a targeted gene of interest and the creation of transgenic mouse containing the same. However, the art also

teaches the resulting phenotype of a knockout mouse is exceedingly unpredictable. For example, Leonard (Immunological Reviews, 1995, 148: 98-114) discloses mice with disruption in the gc gene that was intended to be a model for X-linked severe combined immunodeficiency (XCIDS), but displays a variety of unexpected traits (Abstract). These knockout mice were expected to have thymocytes with decreased proliferation in response to stimulation with antibodies, but the thymocytes proliferated normally (pp 105, line 7). Griffiths (Microscopy Research and Technique 1998, 41: 344-358) taught that, despite a known role for the PLP gene based on spontaneous mutations in the gene, the knockout mouse failed to display any of the expected phenotype (pp 350, last paragraph). Furthermore, the state of the art suggests such unpredictability of phenotype is correlative to the genetic background of the knockout mouse. For example, Keri et al., (Proc Natl Acad Sci U S A. 2000; 97(1): 383-7) show that elevated levels of lutenizing hormone in transgenic can result in different reproductive system abnormalities including ovarian tumors. Schoonjans et al (Stem Cells, 2003; 21:90-97), for example state that the phenotype of gene-targeted mice is not only due to genetic alteration itself but also to the genetic background in which it is generated (pp93, discussion). Similarly, Wolfer et al (Trends in Neuroscience, 2002, 25 (7): 336-340) describe the unpredictability of phenotype resulting from gene disruption can influenced by gene flanking the disrupted coding sequence and by the general genetic background of mouse strains, wherein congenic strains carrying the same null mutation can sometime show widely divergent phenotypes (pp 336, column 1-3). Furthermore, mere capability to perform gene transfer in a mouse is not enabling because a desired

phenotype cannot be predictably achieved by simply introducing transgene construct as recited in the claims. Holschneider et al. (Int J Devl Neuroscience, 2000, 18: 615-618) state that single genes are often essential in a number of different physiological processes. Hence, deletion of an individual gene may prove so drastic or so widespread as to create an amalgam of phenotypes whose interpretation becomes confounded by the interaction of various new physiologic changes (pp 615). Holschneider et al discuss various factors that contribute to the resulting phenotype of transgenic mice, including compensatory system that may be activated to mask the resulting phenotype; these compensatory changes may be due to differential expression of another gene, which may be regulated by the downstream product of the deleted gene.

Thus, at the time of filing, it is evident from the art of record that the resulting phenotype of a homozygous and heterozygous knockout was considered unpredictable and the specification does not provide any evidence to suggest a specific phenotype for opn+/- heterozygous mouse. The guidance provided by the specification amounts to invitation for the skilled Artisan to try and follow the disclosed instructions to make and use the claimed invention.

As a second issue, claims 5-7 embrace a method for identifying a therapeutic agent for modulating circadian rhythm in a mammal by administering an agent to a transgenic knockout animal whose genome comprises a disruption in its endogenous melanopsin gene, wherein the disruption prevents the expression of a functional melanopsin protein in cells of the animal. The specification teaches a circadian rhythm phenotype in a transgenic knockout mouse whose genome comprises a homozygous

disruption of endogenous melanopsin gene such that no functional protein is made, however, specification does not provide any guidance or working example to show feasibility of any other transgenic knockout animal with disclosed phenotype (see pages 22-29). Prior to instant invention, the art teaches method of making transgenic nonhuman animal from ES technology was not predictable for any species other than mouse. Since the specification discloses using mouse ES cells to produce transgenic OSP4-/- knockout mice via homologous recombination of targeting vectors in the ES cells, ES cells from various species are required to produce various nonhuman animal. However, Houdebine, 1994 (Journal of Biotechnology, Vol., 34, pp 269-287) describes that although ES cells can be used to generate transgenic animals, but this approach remains restricted to mice, ES cells from other species are not presently available (pp 279, column 1, line 7-8). Furthermore Mullin et al also point that non-mouse ES cell capable of providing germ line chimeras were not available (Mullins et al., Journal of Clinical Investigation, 1996, pp 1557, 1st paragraph). Thus, the state of the art is such that ES cell technology is generally limited to the mouse system and that only putative ES cells exist for other species (Moreadith et al., J. Mol. Med., 1997 p214, abstract). In fact, even after filing of instant application, Hochepied et al (Stem Cells, 2004, 22: 441-447) state "transmission of the genotype to the offspring of chimeras has only been achieved with mouse ES cells (pp 444, right column, lines 1-3). Therefore, at the time of filing of this application, transgenic animal could not be accomplished for any species other than mouse. The specification fails to provide sufficient guidance to make transgenic other than mice by teaching obtaining ES cells in species other than mice.

The specification does not teach how to make other transgenic animal for any other species other than mice or correlate making mice to making transgenic for any other species. Therefore, the claims should be limited to identifying agents in the transgenic mouse as disclosed in the specification. Furthermore, the specification does not provide adequate correlation between phenotype obtained in the mice to the phenotype obtained in other species.

As a third issue, claims 3, 5-8 embrace a transgenic knockout mouse comprising a homozygous disruption in melanopsin gene showing attenuated circadian rhythm phase shift in response to light pulse during a dark portion of an environmental dark/light cycle. It is noted that, Münch et al (Am J Physiol Regul Integr Comp Physiol 290 R1421-R1428, 2006) in a post filing art conclude wavelength-dependent effects of light on sleep architecture and EEG spectra in men. Münch et al show these effects are small but specific. The studies by Münch provide evidence that evening light exposure affects human physiology, including sleep, and is dependent not only on duration and intensity but also on its wavelength via the non-image-forming (page R1437, col. 2, para 4). In the instant case, claims 3, 5-7 recite phase shift to light response to a light pulse during dark portion of an environmental dark/light cycle. The specification teaches quality of the light pulse can vary and the intensity of the light pulse could vary between 0.001 and 1.5 lux, while high intensity light of greater than 1.5 lux or a monochromatic light of around 480 nm (page 16, lines 16-19). As recited instant claims do not suggest whether light pulse is monochromatic or polychromatic, since prior art suggest effect of light could alter circadian rhythm depending on intensity and wavelength, it is not

apparent whether applicants claims as recited would show any attenuated phenotype in mouse as recited in response to any light pulse.

As a final issue, the function of melanopsin gene product has been speculated to be localized to the inner layer of the retina, within ganglion and amacrine cells (Beaule et al, Journal of Molecular Neuroscience, 2003, 73-89, page 75, col. 1, para 2) which is considered circadian photo receptor (abstract). However, post filing art summarized by the reference of Beaule et al (Journal of Molecular Neuroscience, 2003, 73-89) suggest melanopsin in itself is not necessary for circadian photoreception. Beaule states, " In fact it appears that within the photoreceptive system there is some degree of redundancy, each contributing in some way to photoic entrainment"(abstract). In addition, Kavakli et al (Mol Interv. 2002 Dec;2(8):484-92) while reviewing the role of melanopsin as a possible circadian photoreceptor states " Melanopsin knockout mice have recently been generated to analyze this hypothesis. The animals entrain normally to LD cycles, show phase shifting in response to short light pulses, and manifest normal photic induction of clock genes in the SCN. It appears, however, that under dim light, the magnitude of phase shifts is moderately reduced relative to wild-type animals. Assuming that this effect is not due to differences between mouse strain backgrounds, it appears that melanopsin either directly or indirectly plays a minor role in circadian photoreception"(page 488, col. 2, see melanopsin knockout mice section). The cited art clearly shows only marginal role of melanopsin gene in regulating circadian rhythm. The art of record fail to establish this relationship and the specification lacks any teaching that establishes the function of melanospin in modulating circadian rhythm phase shift in

any animal in response to any light pulse. In the instant case, claimed invention recite a phenotype, which may not be related to melanopsin knockout given the unpredictability in the phenotype and influence of genetic background on phenotype an artisan for the specific reasons cited above it would have required undue experimentation for an artisan of skill to make and use the claimed invention.

In conclusion, in view of breadth of the claims and absence of a strong showing by applicant, in the way of specific guidance and direction, and/or working examples demonstrating the same, such invention as claimed by applicant is not enabled for the claimed inventions commensurate with the full scope of the claims. The specification and prior art do not teach "any" transgenic animal for the claimed method. An artisan of skill would have required undue experimentation to practice the method as claimed because the art of making nonhuman transgenic other then mice and phenotype was unpredictable at the time of filing of this application as supported by the observations in the art record.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-2 and 4 are rejected under 35 U.S.C. 103(a) as being unpatentable over Provencio et al (The Journal of Neuroscience, 2000, 20(2): 600-605), Capecchi (US patent no. 5,464,764, November 7, 1995) and Genebank number GenBank Accession Number AF_147789, dated 1/15/2000).

Claims 1-2 and 4 are drawn to a transgenic mouse comprising a disruption in an endogenous melanopsin gene, such that no functional melanopsin protein is made in cells of the mouse. Claim 2 limits the transgenic mouse of claim 1 to include homozygous deletion of melanopsin gene. Claim 4 is directed to a cells isolated from the mouse of claim 1, wherein genome of the cell comprises a disruption in its endogenous melanopsin gene, and wherein the homozygous disruption prevents the expression of a functional melanopsin protein in said cell.

Provencio et al teach a novel human opsin, melanopsin that is expressed in cells of the mammalian inner retina (abstract). It is noted that Provencio et al suggest presence of melanopsin in the inner retina raises the possibility that some mammalian ganglion and amacrine cells are directly photosensitive. Provencio et al also disclose that action spectra of rodent circadian responses more closely resemble the spectral absorbance profile of opsin-based photopigments rather than flavin-based cryptochromes. It is noted that Provencio et al contemplate only melanopsin as one of the four known mammalian non-visual opsins that is expressed by cells in the ganglion and amacrine cell layers of the retina and thus, this unique anatomical localization, coupled with the known action spectra for mammalian circadian photo regulation, makes

melanopsin a viable candidate as a mammalian circadian photo pigment. However, Provencio et al do teach a melanopsin knock out mouse.

Capecchi taught knockout technology as it relates to mice and application of the technology to any known gene of interest but specifically with respect to HoxA-3 gene. Capecchi taught the use of the mice in determining the *in vivo* biological function of any known gene of interest (see column 6, line 59, column 7, line 5; Column 12, lines 39-42 and 47-48). For example, Capecchi discloses the applicability of gene targeting to many other genes that a correlation can be drawn between the disruptions of the gene to the manifestation of the disease symptoms (see column 12, line 47 and column 12, line 7). Capecchi further discloses the essential components of a targeting vector including a selectable marker genes such as that encoding neomycin resistance (column 6, line 50-58, column 7, lines 17-28; table 1, Figure 1), and the steps involved for targeted gene replacement in ES cells, and in turn in mice (column 15, line 59-column 16, line 9). Capecchi taught that the vectors could be used to produce transgenic animals, using transfected mouse ES cells (see column 15, lines 59-67). The transfected ES cells are combined with a mouse blastocyctes where they contribute to the germ line of the resulting chimeric animal (column 16, lines 1-10). Capecchi clearly shows that the vectors and methods can be used for any known gene of interest. It is noted that Capecchi et al also teach southern blot in somatic cells from the offspring of the transgenic mouse to show the disrupted gene is transferred to the offspring. However, Capecchi et al do not teach targeting construct-comprising sequence necessary to target melanopsin gene.

Prior to claimed invention, GenBank Accession Number AF_147789 taught the sequence of the melanopsin gene.

It would have been obvious to one of ordinary skill in the art at the time of invention was made to study the physiological role of melanopsin gene as described by Provencio in a melanopsin deficient mice by combining the teaching of Capecchi with those of GenBank Accession number AF_147789 to make a transgenic comprising a disruption in the claimed melanopsin gene. One of skill in the art would have been motivated to make a knockout mice using the method of Capecchi comprising a disruption of melanopsin gene for the purpose of determining the physiological role of melanopsin in circadian rhythm disorder as speculated by Provencio. Furthermore, Capecchi taught using mice to determine the function of the gene of interest and screen for therapies to treat conditions caused by the gene disruption (column 12-13, bridging paragraph). One of the skill in art would have been also motivated to isolate cell lines from the mouse, as recited in the claims, to perform in vitro assays of agents that restore activity of downstream genes in search of therapeutic agents to treat diseases modeled by the gene knockout (Capecchi, column 12-13).

One of the ordinary skills in the art would expect a reasonable expectation of success in combining the teaching of Capecchi with GenBank Accession number AF_147789, because it was routine in the art at the time of filing to apply method of Capecchi to any gene of interest.

Therefore, the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention.

It is emphasized that rejected claims comprises knockout mouse that do not require any specific phenotype, in addition any observed phenotype in these disclosed mouse may not be specific to the disruption of the endogenous melanopsin gene.

Conclusion

No Claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anoop Singh whose telephone number is (571) 272-3306. The examiner can normally be reached on 9:00AM-5:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272- 0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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